

11. BIAS INVESTIGATION

11.1 Introduction

Any study of reproductive outcomes will produce biased results if children are misclassified according to birth defect status. In this study, we addressed this source of bias through medical record verification of every child, regardless of parental opinion regarding birth defects. The verification process has eliminated the possibility of reporting bias. Nevertheless, bias may occur due to differential verification of the children. Differential verification might occur if, as a result of media publicity, Ranch Hand parents asked physicians to look for birth defects during routine visits, actively sought medical opinion regarding potential defects, or directed Air Force investigators to medical records that documented defects in favor of those records that did not document defects, while Comparison parents did not exhibit this behavior. Differential verification of this kind would not affect analyses involving only Ranch Hands (Models 1 and 2) because all Ranch Hands were blinded to their dioxin result prior to and during the verification process. Differential verifiability might, however, affect analyses based on Model 3. In this section rates are expressed per 1000 children.

11.2 Analysis

Four sources were used, in various combinations, to verify conception outcome and birth defect status. They were: birth certificates, newborn clinic records, health records and death certificates. Counts of children with verified defects fathered by participants included in Models 1, 2 or 3 according to these sources and their combinations are shown in Table 11-1, categorized by the father's group membership (Ranch Hand, Comparison) and time of conception relative to the father's duty in SEA (pre-SEA, post-SEA).

Table 11-1

**Counts of Verified Defective Children Included in
Models 1, 2 or 3 by Source of Record,
Fathers Group Membership and Time of Conception**

Source	Time of Conception Relative to the Father's Duty in SEA			
	Pre-SEA		Post-SEA	
	Ranch Hand (n=1283)	Compar- ison (n=1459)	Ranch Hand (n=791)	Compar- ison (n=981)
Birth certificate only	0	0	0	0
Death certificate only	0	1	0	0
Birth and death certificates	0	0	0	0
Birth and death certificates and health records	1	0	0	0
Death certificate and newborn clinic	0	0	0	0
Death certificate and newborn clinic and health records	0	0	0	0
Death certificate and birth certificate and newborn clinic	1	0	0	0
Death certificate and birth certificate and newborn clinic and health records	3	0	0	0
Birth certificate and health records	31	48	26	27
Newborn clinic only	1	3	3	3
Newborn clinic and health records	3	5	11	17
Birth certificate and newborn clinic	19	22	28	28
Birth certificate and newborn clinic and health records	68	58	92	103
Health records only	5	9	7	12
Death certificate and health records	0	1	0	0
Death certificate and birth certificate and newborn clinic and health records plus death certificate	0	1	0	0
Birth certificate and newborn clinic and health records plus death certificate and birth certificate and newborn clinic	1	1	0	1
Birth certificate and death certificate plus death certificate	0	0	1	0
Birth certificate and death certificate and health records plus birth certificate and newborn certificate	0	1	0	0

Table 11-1 (Continued)

Source	Time of Conception Relative to the Father's Duty in SEA			
	Pre-SEA		Post-SEA	
	Ranch Hand (n=1283)	Compar- ison (n=1459)	Ranch Hand (n=791)	Compar- ison (n=981)
Birth certificate and newborn clinic and health records and death certificate plus birth certificate and newborn clinic	1	0	0	0
Birth certificate and newborn clinic and health records plus birth certificate and newborn clinic and health records and death certificate	1	1	0	2
Birth certificate and newborn clinic and health records plus birth certificate and newborn clinic	3	4	7	9
Newborn clinic and health records plus newborn clinic	0	1	0	2
Birth certificate and health records plus death certificate	1	1	0	0
Birth certificate and health records plus health records	0	1	0	0
Birth certificate and health records and death certificate plus birth certificate	0	0	1	0
Birth certificate and newborn clinic and health records plus birth certificate and newborn clinic plus birth certificate and newborn clinic and death certificate	1	0	0	0
Total	140	158	176	204

We assume that parents have no control over the existence or content of birth certificates, newborn clinic records or death certificates. Parents might influence the existence or content of health records, however, through elective health care and pointed requests to physicians to find and annotate birth defects. Hence all combinations of sources involving health records might be subject to this bias, although the phenomenon might be expected to occur most often in children with no other corroborating source (health records only) because, presumably, the parents would know that the birth defect was already noted on the birth certificate or in the newborn clinic records and would therefore not be inclined to seek further documentation from a physician.

Pre-SEA and Post-SEA counts and rates are presented in Table 11-2 and odds ratios and associated test statistics are presented in Table 11-3 for all sources involving health records and for health records only.

Table 11-2

Pre-SEA and Post-SEA Counts and Rates by Source of Record and the Father's Group Membership Among Children Whose Father Entered any of Model 1, 2 or 3 Analyses

Source	Time of Conception Relative to the Father's Duty in SEA			
	Pre-SEA		Post-SEA	
	Ranch Hand Count(Rate)	Comparison Count(Rate)	Ranch Hand Count(Rate)	Comparison Count(Rate)
All combinations of sources involving health records	119 (92.8)	132 (90.5)	144 (182.0)	173 (176.4)
Health records only	5 (3.9)	9 (6.2)	7 (8.8)	12 (12.2)

Without adjustment for covariates (Table 11-3), there is no significant variation in the association between source of record (all combinations of sources involving health records versus all other sources) and the father's group membership (Ranch Hand, Comparison) with time of conception relative to duty in SEA ($p=0.950$). Furthermore, there is no significant association between source of record and father's group membership among pre-SEA ($p=0.836$) or among post-SEA ($p=0.756$) conceptions. After restriction to health records only, there is no significant variation in the association between source of record and the father's group membership with time of conception relative to duty in SEA (pre-SEA odds ratio=0.63, post-SEA odds ratio=0.72, $p=0.855$). There is no significant association between source of record and the father's group membership among pre-SEA ($p=0.405$) or post-SEA ($p=0.492$) children.

Table 11-3

**Pre-SEA and Post-SEA Odds Ratios Relating Source of Record
and the Father's Group Membership Among Children Whose Father
Entered any of Model 1, 2 or 3 Analyses**

Source	Time of Conception Relative to the Father's Duty in SEA				Test for Equality of Odds Ratios p-value
	Pre-SEA		Post-SEA		
	Odds Ratio	p-value	Odds Ratio	p-value	
All combinations of sources involving health records	1.03	0.836	1.04	0.756	0.950
Health records only	0.63	0.405	0.72	0.492	0.855

Verification bias, if it exists, might be most prominent in children who were at least one month old when the Agent Orange publicity began to peak in early 1978. Hence, the significance of the association between source of record and the father's group membership was assessed with the source of record being any combination involving health records and health records only for children aged one month or older on 1 January 1978 (born on or before 1 December 1977). The results are summarized in Table 11-4 and 11-5.

Table 11-4

Pre-SEA and Post-SEA Counts and Rates by Source of Record and the Father's Group Membership Among Children Aged One Month or Older on 1 January 1978 and Whose Father Entered any of Model 1, 2 or 3 Analyses

Source	Time of Conception Relative to the Father's Duty in SEA			
	Pre-SEA		Post-SEA	
	Ranch Hand Count(Rate)	Comparison Count(Rate)	Ranch Hand Count(Rate)	Comparison Count(Rate)
All combinations of sources involving health records	119 (92.3)	132 (90.5)	105 (173.8)	122 (168.5)
Health records only	5 (3.9)	9 (6.2)	5 (8.3)	10 (13.8)

Without adjustment for covariates (Table 11-5) and with restriction to children aged one month or older on 1 January 1978, there is no significant variation in the association between source of record (all combinations involving health records versus all other sources) and the father's group membership (Ranch Hand, Comparison) with time of conception relative to duty in SEA ($p=0.959$). Furthermore, there is no significant association between source of record and the father's group membership among pre-SEA ($p=0.836$) or among post-SEA ($p=0.797$) conceptions. After restriction to health records only, there is no significant variation in the association between source of record and the father's group membership with time of conception relative to duty in SEA (pre-SEA odds ratio=0.63, post-SEA odds ratio=0.60, $p=0.943$). There is no significant association between source of record and the father's group membership among pre-SEA ($p=0.405$) or post-SEA ($p=0.342$) children.

Table 11-5

Pre-SEA and Post-SEA Odds Ratios Relating Source of Record and Fathers
Group Membership Among Children Aged One Month or Older on 1 January 1978
Whose Father Entered any of Model 1, 2 or 3 Analyses

Source	Time of Conception Relative to the Father's Duty in SEA				Test for Equality of Odds Ratios p-value
	Pre-SEA		Post-SEA		
	Odds Ratio	p-value	Odds Ratio	p-value	
All combinations of sources involving health records	1.03	0.836	1.04	0.797	0.959
Health records only	0.63	0.405	0.60	0.342	0.943

As a final bias assessment, the possibility that children of fathers who gave blood for the dioxin assay might be more or less likely to exhibit birth defects than children of fathers who did not provide blood for the dioxin assay was investigated because only children whose father had a valid serum dioxin result were included in the analyses summarized in this report. To this end, all 6792 verified biologic children of Ranch Hands and Comparisons were classified as having a verified birth defect if the defect was verified and satisfied the CDC definition of total congenital anomaly. The fathers were categorized as assayed or not assayed according to whether they did or did not give blood for the serum dioxin assay (regardless of the result of the assay). These data were further categorized by the father's group (Ranch Hand, Comparison), the time of conception of the child (pre-SEA, post-SEA) and the father's military occupation in SEA (officer, enlisted flyer, enlisted ground personnel). These data are summarized in Table 11-6.

Table 11-6

**Cross Classification of 6792 Verified Biologic Children
by Birth Defect, Time of Conception and the Father's
Assay Status, Group and Military Occupation**

a) Children of Fathers Not Assayed for Dioxin

Time of Conception	Father's Occupation	Group	Children		Rate (per 1000)
			with Birth Defects	Total	
Pre-SEA	Officer	RH	18	174	103.4
		C	28	264	106.1
	Enlisted Flyer	RH	10	79	126.6
		C	17	128	132.8
	Enlisted Ground	RH	10	172	58.1
		C	22	264	83.3
Post-SEA	Officer	RH	19	65	292.3
		C	17	154	110.4
	Enlisted Flyer	RH	7	24	291.7
		C	10	36	277.8
	Enlisted Ground	RH	18	118	152.5
		C	25	250	100.0

Table 11-6 (Continued)

b) Children of Fathers Assayed for Dioxin

Time of Conception	Father's Occupation	Group	Children		Rate (per 1000)
			with Birth Defects	Total	
Pre-SEA	Officer	RH	71	678	104.7
		C	104	832	125.0
	Enlisted Flyer	RH	35	301	116.3
		C	35	349	100.3
	Enlisted Ground	RH	40	401	99.8
		C	48	503	95.4
Post-SEA	Officer	RH	33	204	161.8
		C	77	344	223.8
	Enlisted Flyer	RH	25	97	257.7
		C	24	119	201.7
	Enlisted Ground	RH	127	537	236.5
		C	136	699	194.6

A log-linear analysis of these data found significant variation in the association between birth defects and assay status with the father's military occupation in SEA ($p=0.008$) and no significant variation with the father's group. This interaction is summarized in Table 11-7.

Table 11-7

Birth Defects versus the Father's Assay Status
by the Father's Military Occupation in SEA

a) Children of Fathers Not Assayed for Dioxin

The Father's Occupation	Children		Rate (per 1000)
	with Birth Defects	Total	
Officer	82	657	124.8
Enlisted Flyer	44	267	164.8
Enlisted Ground	75	804	93.3

Table 11-7 (Continued)

b) Children of Fathers Assayed for Dioxin

The Father's Occupation	Children		Rate (per 1000)
	with Birth Defects	Total	
Officer	285	2058	138.5
Enlisted Flyer	119	866	137.4
Enlisted Ground	351	2140	164.0

This interaction is primarily due to the difference in birth defect rates in children of enlisted ground personnel who were not assayed (93.3 per 1000) and in children of enlisted ground personnel who were assayed (164.1 per 1000). This difference in rates is statistically significant ($p < 0.001$). The rates did not differ significantly for the officer or enlisted flyer occupation.

This rate difference indicates the presence of selection bias; children of fathers who volunteered for the dioxin assay and who were enlisted ground personnel in Vietnam are more likely to have verified birth defects than children of such fathers who did not volunteer. This difference does not detract from the inferences of this report, however, because the rate is higher in children of assayed fathers than in children of unassayed fathers.

11.3 Conclusion

We considered the possibility that Ranch Hand parents actively sought medical opinion regarding birth defects in their children, making birth defects more verifiable in their children than in Comparison children. We found no evidence of this 'verification' bias. We also investigated selection bias for the dioxin assay and found that children of enlisted ground personnel who volunteered for the assay were more likely to have birth defects than children of enlisted ground personnel who did not volunteer. This difference constitutes a selection bias. However, this bias is not detrimental to this report because the birth defect rate was higher in children of assayed fathers than in children of unassayed fathers.